SUPPLEMENTARY APPENDIX

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CONSORT 2010 checklist of information to include when reporting a randomised trial

Section/Topic	Item No	Checklist item	Reported on page No
Title and abstract			
	1a	Identification as a randomised trial in the title	1
	1b	Structured summary of trial design, methods, results, and conclusions (for specific guidance see CONSORT for abstracts)	4
Introduction			
Background and objectives	2a	Scientific background and explanation of rationale	6-7
	2b	Specific objectives or hypotheses	7
Methods			
Trial design	3a	Description of trial design (such as parallel, factorial) including allocation ratio	7
	3b	Important changes to methods after trial commencement (such as eligibility criteria), with reasons	9
Participants	4a	Eligibility criteria for participants	8, Supp. Appendix (p. 13-15)
	4b	Settings and locations where the data were collected	7
Interventions	5	The interventions for each group with sufficient details to allow replication, including how and when they were actually administered	7
Outcomes	6a	Completely defined pre-specified primary and secondary outcome measures, including how and when they were assessed	9, Supp Methods (p. 16)
	6b	Any changes to trial outcomes after the trial commenced, with reasons	9
Sample size	7a	How sample size was determined	10
	7b	When applicable, explanation of any interim analyses and stopping guidelines	NA
Randomisation:			
Sequence generation	8a	Method used to generate the random allocation sequence	8
	8b	Type of randomisation; details of any restriction (such as blocking and block size)	8
Allocation concealment mechanism	9	Mechanism used to implement the random allocation sequence (such as sequentially numbered containers), describing any steps taken to conceal the sequence until interventions were assigned	8
Implementation	10	Who generated the random allocation sequence, who enrolled participants, and who assigned participants to interventions	8
Blinding	11a	If done, who was blinded after assignment to interventions (for example, participants, care providers, those assessing outcomes) and how	Supp. Methods (p. 16)
	11b	If relevant, description of the similarity of interventions	NA

CONSORT Checklist (cont.)

Statistical methods	12a	Statistical methods used to compare groups for primary and secondary outcomes	10; Supp. Methods (p. 16-17)
	12b	Methods for additional analyses, such as subgroup analyses and adjusted analyses	10; Supp. Methods (p. 16-19)
Results			
Participant flow (a diagram is strongly recommended)	13a	For each group, the numbers of participants who were randomly assigned, received intended treatment, and were analysed for the primary outcome	11; Fig. 1B
	13b	For each group, losses and exclusions after randomisation, together with reasons	11, Fig. 1B
Recruitment	14a	Dates defining the periods of recruitment and follow-up	11
	14b	Why the trial ended or was stopped	NA
Baseline data	15	A table showing baseline demographic and clinical characteristics for each group	Table 1; Table S1
Numbers analysed	16	For each group, number of participants (denominator) included in each analysis and whether the analysis was by original assigned groups	Fig. 1B; Table 2; Table S2
Outcomes and estimation	17a	For each primary and secondary outcome, results for each group, and the estimated effect size and its precision (such as 95% confidence interval)	11-12; Table 2; Table S2; Fig. 2; Supp Results (Fig. S1, p. 21)
	17b	For binary outcomes, presentation of both absolute and relative effect sizes is recommended	Table 2; Table S2
Ancillary analyses	18	Results of any other analyses performed, including subgroup analyses and adjusted analyses, distinguishing pre-specified from exploratory	11-14; Fig. 2; Supp Results (p. 20); Fig. S1
Harms	19	All important harms or unintended effects in each group (for specific guidance see CONSORT for harms)	12; Table 3; Supp Results (p. 20); Table S3; Table S4
Discussion			
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Generalisability	21	Generalisability (external validity, applicability) of the trial findings	15-17
Interpretation	22	Interpretation consistent with results, balancing benefits and harms, and considering other relevant evidence	15-17
Other information			
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Ethics Committees and Protocol Approvals

Title: A phase II, randomized, double-blind, placebo-controlled, multicenter study to evaluate the safety and efficacy of MSTT1041A or UTTR1147A in patients with severe COVID-19 pneumonia

Study number: GA42469

Protocol approval dates:

- United States: 4 April 2020
- Mexico: 8 July 2020 (local ethics committee approved at the first site on 29 Jun 2020)
- Spain: 13 July 2020
- Brazil: 20 July 2020

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Supplementary Methods

Full inclusion and exclusion criteria

Inclusion Criteria:

- Documented informed consent
- Age ≥ 18 years at time of signing Informed Consent Form
- Ability to comply with the study protocol
- Hospitalized with COVID-19 pneumonia confirmed per WHO criteria (including a positive PCR of any specimen; e.g., respiratory, blood, urine, stool, other bodily fluid) and evidenced by chest X-ray or CT scan
- For sites at an altitude ≤ 5000 feet: peripheral capillary oxygen saturation (SpO_2) ≤ 93% or partial pressure of oxygen (PaO_2)/fraction of inspired oxygen (FiO_2) ≤ 300 mmHg or requirement for supplemental oxygen to maintain SpO_2 > 93%
- For sites at an altitude > 5000 feet: requirement for supplemental oxygen to maintain SpO_2 at an acceptable level per local standard of care
- For women of childbearing potential: agreement to remain abstinent (refrain from heterosexual intercourse) or use contraception, as defined below:
    - Women must remain abstinent or use contraceptive methods with a failure rate of < 1% per year during the treatment period and for 95 days after the final dose of study drug.
    - A woman is considered to be of childbearing potential if she is postmenarchal, has not reached a postmenopausal state (≥ 12 continuous months of amenorrhea with no identified cause other than menopause), and is not permanently infertile due to surgery (i.e., removal of ovaries, fallopian tubes, and/or uterus) or another cause as determined by the investigator (e.g., Müllerian agenesis). The definition of childbearing potential may be adapted for alignment with local guidelines or regulations.
    - Examples of contraceptive methods with a failure rate of < 1% per year include bilateral tubal ligation, male sterilization, hormonal contraceptives that inhibit ovulation, hormone-releasing intrauterine devices, and copper intrauterine devices.
    - The reliability of sexual abstinence should be evaluated in relation to the duration of the clinical trial and the preferred and usual lifestyle of the patient. Periodic abstinence (e.g., calendar, ovulation, symptothermal, or postovulation methods) and withdrawal are not adequate methods of contraception. If required per local guidelines or regulations, locally recognized adequate methods of contraception and information about the reliability of abstinence will be described in the local Informed Consent Form.
- For men: agreement to remain abstinent (refrain from heterosexual intercourse) or use a condom, and agreement to refrain from donating sperm, as defined below:
    - With a female partner of childbearing potential or pregnant female partner, men must remain abstinent or use a condom during the treatment period and for 95 days after the final dose of study drug to avoid exposing the embryo. Men must refrain from donating sperm during this same period.

- The reliability of sexual abstinence should be evaluated in relation to the duration of the clinical trial and the preferred and usual lifestyle of the patient. Periodic abstinence (e.g., calendar, ovulation, symptothermal, or postovulation methods) and withdrawal are not adequate methods of preventing drug exposure. If required per local guidelines or regulations, information about the reliability of abstinence will be described in the local Informed Consent Form.

Exclusion Criteria:

- Pregnant or breastfeeding, or intending to become pregnant during the study or within 95 days after the final dose of study drug
  - Women of childbearing potential must have a negative pregnancy test at screening
- Any serious medical condition or abnormality of clinical laboratory tests that, in the investigator's judgment, precludes the patient's safe participation in and completion of the study
- In the opinion of the investigator, progression to death is imminent and inevitable within the next 24 hours, irrespective of the provision of treatments
- Participating in another clinical drug trial
- Treatment with investigational therapy (other than for COVID-19) within 5 half-lives or 30 days (whichever is longer) prior to initiation of study drug
- Use of Janus kinase (JAK) inhibitor within 30 days or 5 drug elimination half-lives (whichever is longer) prior to screening
- Have received high-dose systemic corticosteroids (≥1 mg/kg/day methylprednisolone or equivalent) within 72 hours prior to day 1
- Known HIV infection with CD4 < 200 cells/mL or < 14% of all lymphocytes
- ALT or AST > 10 x upper limit of normal (ULN) detected at screening
- History of anaplastic large-cell lymphoma or mantle-cell lymphoma
- History of cancer within the previous 5 years unless it has been adequately treated and considered cured or remission-free in the investigator's judgment
- Clinical evidence of active or unstable cardiovascular disease (e.g., acute myocardial ischemia or decompensated heart failure) as assessed by the investigator
- Elevated cardiac troponin indicative of a recent cardiac event or myocarditis/pericarditis, as defined below:
  - If high-sensitivity immunoassay is available locally: high-sensitivity troponin (hs-troponin) I or T > ULN (as per local standard for ULN), unless certain additional criteria are met, as outlined below:
    - If the local laboratory reports "indeterminate" or "intermediate" hs-troponin results: Patients with hs-troponin in the "intermediate" or "indeterminate" range (per local laboratory) may be enrolled if an echocardiogram shows normal left ventricular ejection fraction (as per local standard for normal, generally 50%-55%) without evidence of hypokinesis; if an echocardiogram cannot be obtained, clinical evaluation excluding myocarditis/pericarditis is acceptable.
    - If the local laboratory does not report "indeterminate" or "intermediate" hs-troponin results: Patients with hs-troponin > ULN to < 5 x ULN may be enrolled if an echocardiogram shows normal left ventricular ejection fraction (as per local

standard for normal, generally 50%-55%) without evidence of hypokinesis; if an echocardiogram cannot be obtained, clinical evaluation excluding myocarditis/pericarditis is acceptable.

- If high-sensitivity immunoassay is not available locally: conventional cardiac troponin I or T > ULN, (based on local standard for ULN)
  - Patients with screen failure due to conventional troponin > ULN may be re-screened and enrolled if a repeat conventional troponin is ≤ULN and an echocardiogram shows normal left ventricular ejection fraction (as per local standard for normal, generally 50%-55%) without evidence of hypokinesis; if an echocardiogram cannot be obtained, clinical evaluation excluding myocarditis/pericarditis is acceptable.

- History or presence of an abnormal ECG that is clinically significant in the investigator's opinion, including complete left bundle branch block, second- or third-degree atrioventricular heart block, or evidence of prior myocardial infarction
- Sustained prolongation of QT interval corrected through use of Fridericia's formula (QTcF), defined as repeated demonstration of QTcF > 480 ms (NCI CTCAE Grade 1)
  - Patients with prolonged QTcF due to a reversible cause (e.g., electrolyte abnormalities) may be re-tested after the underlying cause has been corrected.
  - For patients with a ventricular pacemaker, there should be appropriate correction for heart rate and pacing when determining baseline QTcF (as per Chakravarty et al. 2015); absolute QTcF values should not exceed 490 ms.
- History of ventricular dysrhythmias or risk factors for ventricular dysrhythmias such as structural heart disease (e.g., severe left ventricular systolic dysfunction, hypertrophic cardiomyopathy or arrhythmogenic right ventricular cardiomyopathy), coronary heart disease (symptomatic or with ischemia demonstrated by diagnostic testing), or family history of sudden unexplained death or long QT syndrome
- History of moderate or severe allergic, anaphylactic, or anaphylactoid reactions or hypersensitivity to any component of study treatment

Additional blinding information

Patients, study site personnel, and the sponsor study team remained blinded to individual treatment assignments. A data monitoring committee reviewed unblinded safety and study conduct data throughout the study. Pharmacokinetic samples were collected from patients assigned to the placebo arm to maintain the blinding of treatment assignment, and laboratory personnel responsible for performing study drug pharmacokinetics and anti-drug antibody (ADA) assays were unblinded to patient treatment assignments to identify appropriate samples for analysis.

Additional secondary endpoints

Additional secondary endpoints were the time to improvement of at least 2 categories relative to baseline on the 7-category ordinal scale of clinical status; the duration of supplemental oxygen; clinical status assessed using the 7-category ordinal scale at days 14 and 28; time to clinical failure, defined as the time to death, mechanical ventilation, ICU admission, or withdrawal of care (for patients entering the study already in ICU or on mechanical ventilation, clinical failure was defined as a one-category worsening on the ordinal scale, withdrawal, or death); and time to clinical improvement, defined as a National Early Warning Score 2 (NEWS2) of ≤2 maintained for 24 hours.

Statistical methods: secondary endpoints

For clinical status assessed using the 7-category ordinal scale, the proportion of patients with a response in each category of the ordinal scale was summarized by treatment groups at time points of interest.

Time-to-event secondary endpoints were analyzed similarly to the primary endpoint. For time-to-event endpoints other than time to clinical failure, deaths were right censored at day 28. For time to clinical improvement, patients discharged from the hospital without clinical improvement were censored at the day of their last observed assessment. For patients that were discharged without an ordinal score assessment at discharge, they were assumed to have an ordinal score of 1 on the day of discharge.

Secondary endpoints describing incidence were analyzed using the Cochran-Mantel-Haenszel (CMH) test statistics, adjusting for stratification factors.

Secondary endpoints describing duration were analyzed using the stratified Wilcoxon Rank Sum test, adjusting for stratification factors.

The number of ventilator-free days (VFDs) was defined as the number of days during the 28-day treatment period when the patient was alive and without need for invasive mechanical ventilation. For any day during day 1 and day 28, if invasive mechanical ventilation or ECMO was recorded for any part of the day (≥ 12 hours during mechanical invasive ventilation for patients with tracheostomy), the day was not counted as a VFD; otherwise, the day was counted. For any days prior to day 28 where status of mechanical ventilator was missing, the last known status was carried forward. The total number of days was the sum of all VFDs,

regardless of whether the days occurred consecutively or in nonconsecutive intervals. Special considerations for calculating VFD include the following:

- For patients who were on an invasive mechanical ventilator from day 1 to day 28, their VFDs were zero if they completed the study on or prior to day 28.
- For patients who discontinued from the study early while being on invasive mechanical ventilator, their remainder of the days, i.e., from the day of discontinuation to day 28, were not counted as VFDs.
- For patients who discontinued from the study early without being on invasive mechanical ventilator, their remainder of the days, i.e., from the day of discontinuation to day 28, were counted as VFDs.
- For patients who died on or prior to day 28, their VFDs were zero.

Duration of ICU stay was calculated as the total number of hours spent in the ICU up to and inclusive of 28 days. If ICU admission occurred before randomization, the ICU duration was counted from the date of dosing. Partial admission and discharge date/time were imputed following a conservative approach. For each patient, durations of multiple ICU stays were summed. Special considerations for calculating ICU duration include the following:

- For patients who discontinued from study early and were in the ICU on the day of discontinuation, they were assumed to be in the ICU for the remainder of the days, i.e., from the day of discontinuation to day 28.
- For patients who discontinued from the study early and were not in the ICU on the day of discontinuation, they were assumed to have no incidence of ICU after discontinuation.
- For patients who were discharged from the hospital, any ongoing ICU stays without an ICU discharge date/time were imputed from the date/time of hospital discharge. The discharged patients were assumed to have no incidence of ICU stay after discharge.
- For patients who die on or prior to day 28, their duration of ICU stay was 28 days.

Duration of supplemental oxygen was defined as the number of days during the 28-day treatment period when the patient was alive and received “supplemental oxygen or other forms of ventilation.” For each patient, the duration of multiple non-consecutive periods during which the patient received supplemental oxygen were summed. For any days prior to day 28 where status of supplemental oxygen use was missing, the last known status was carried forward. Special considerations for calculating the duration of supplemental oxygen include the following:

- For patients who discontinued from study early and were on supplemental oxygen on the day of discontinuation, they were assumed to receive supplemental oxygen for the remainder of the days, i.e., from the day of discontinuation to day 28.
- For patients who discontinued from study early and were not on supplemental oxygen on the day of discontinuation, they were assumed not to receive supplemental oxygen for the remainder of the days, i.e., from the day of discontinuation to day 28.
- For patients who died on or prior to day 28, their duration of supplemental oxygen was 28 days.

Additional safety analysis

Investigators assessed causality as “related” or “not related” to study drug independently for blinded astegolimab and blinded efmarodocokin alfa. Safety analyses were conducted on all patients who received at least one dose of study drug, with patients grouped according to the treatment received.

We also monitored adverse events of special interest. While some preclinical evidence demonstrates a potential cardioprotective role for the IL-33/ST2 axis (1-5), other preclinical studies conflict with these findings (6-8). We therefore examined the incidence of major adverse cardiac events (MACEs) in astegolimab-treated patients by analyzing all events under the system organ class of cardiac disorders. Because of previously observed dermatologic AEs after administration of efmarodocokin alfa in a phase 1a study (9), we also monitored the incidence and severity of skin-related AEs.

Pharmacokinetic analysis

The pharmacokinetic objective for this study was to characterize the astegolimab and efmarodocokin alfa pharmacokinetic profiles. The pharmacokinetic analysis population consisted of patients who received at least one dose of astegolimab or efmarodocokin alfa and had sufficient data to enable estimation of key parameters, with patients grouped according to treatment received. Serum samples were collected from all patients prior to the dose on dosing days (day 1 and, if applicable, day 15) and several time points postdose. Astegolimab was measured in serum by enzyme-linked immunosorbent assay (ELISA). Efmarodocokin alfa was quantified using hybrid immunoaffinity capture with liquid chromatography with tandem mass spectrometry (LC-MS/MS) detection. Pharmacokinetic parameters were derived by non-compartmental analysis using Phoenix WinNonlin® 8.2 (Certara, USA, Inc.).

Immunogenicity analysis

The immunogenicity of astegolimab and efmarodocokin alfa was assessed using validated antibody-bridging ELISAs to detect the presence of ADAs in pre-dose and post-dose samples. ADA screening assays were optimized to tolerate drug interference and were able to detect 150 ng/mL of the surrogate positive control sample in the presence of 100 µg/mL astegolimab, and 350 ng/mL of the surrogate positive control sample was detectable in the presence of 10 µg/mL efmarodocokin alfa.

Biomarker measurements

sST2

Serum sST2 was measured using the Quantikine® ELISA Human ST2/IL-33R Immunoassay kit (R&D Systems).

CRP

CRP serum concentrations were measured on a Roche/Hitachi cobas c (cobas®) system. A particle-enhanced immunoturbidimetric assay using human CRP agglutinates with latex particles coated with monoclonal anti-CRP antibodies was performed according to the

manufacturer's instructions (CRPL3; C-reactive protein Gen.3, Roche Diagnostics). Lower limit of quantification (LLOQ): 0.6 mg/L.

REG3A

REG3A serum concentrations were measured as previously described (9) by a qualified ELISA using a commercially available kit developed for human from Dynabio (Marseille, France). All samples were run according to manufacturer specifications (LLOQ: 0.15 ng/mL).

Supplementary Results

Additional safety analysis: related SAEs and AEs of special interest

There were no related SAEs in the placebo group. Two (2%) patients in the astegolimab group had SAEs (one patient with liver injury and one patient with gastric ulcer hemorrhage) deemed related to astegolimab and 2 patients (2%) in the efmarodocokin alfa group had SAEs deemed related to efmarodocokin alfa (one patient with a urinary tract infection and septic shock and one patient with a urinary tract infection). Relatedness was determined by the site investigator.

There were no major imbalances in AEs of special interest, including major adverse cardiac events (MACEs) in the astegolimab arm or Grade ≥3 dermatologic reactions in the efmarodocokin alfa arm. Although investigators reported more patients with MACEs in the astegolimab arm (4 [3.1%]) compared with placebo (2 [1.5%]), an analysis of events under the system organ class of cardiac disorders showed no significant imbalance between the two arms. In the efmarodocokin alfa arm, no concerning on-target AEs occurred, but there were more related AEs primarily driven by events in the investigations (efmarodocokin alfa, 6 [4.5%]; placebo, 3 [2.2.%]) and dermatological (efmarodocokin alfa, 15 [11.4%]; placebo, 8 [6.0%]) system organ classes.

Immunogenicity

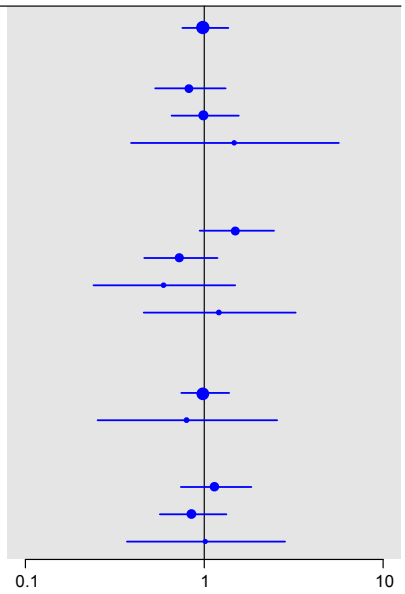
The prevalence of ADAs to astegolimab was 2.8% (5 out of 171 subjects), with 3.4% in the placebo group (2 out of 57 patients) and 2.6% in the treatment group (3 out of 114 patients). The ADA incidence rate was 2.9% (3 out of 104 subjects). Among the three patients in the treatment group with a post-baseline ADA-positive sample, two patients had treatment-induced ADAs, and one patient had treatment-enhanced ADAs. One patient was positive for ADAs at baseline that were unaffected by treatment.

The prevalence of ADAs to efmarodocokin alfa in this study was 1.6% (3 out of 185 subjects) and the ADA incidence rate was 0.9% (1 out of 107 subjects). Two subjects were positive for ADAs at baseline that were unaffected by treatment. For both astegolimab- and efmarodocokin alfa-treated patients, ADAs had no obvious impact on pharmacokinetics, pharmacodynamics, safety, or efficacy.

Supplementary Figures

A

Baseline risk factors	Total n	Placebo n	Placebo Events	Placebo Median (day)	Astegolimab n	Astegolimab Events	Astegolimab Median (day)	Hazard Ratio	95% Wald CI
All	264	134	93	10	130	94	11	1.01	(0.75, 1.36)
Baseline ordinal score									
3	96	47	44	5	49	47	6	0.84	(0.53, 1.32)
4	135	71	45	14	64	42	15	1.01	(0.66, 1.56)
5−6	25	13	4	NA	12	5	NA	1.48	(0.39, 5.66)
<Missing>	8	3	0	NA	5	0	NA	NA	(NA, NA)
Baseline BMI									
<30	101	54	34	11.5	47	39	9	1.52	(0.94, 2.46)
≥30 to < 40	106	55	42	10	51	33	12	0.74	(0.46, 1.19)
≥40	27	10	9	12	17	12	14	0.6	(0.24, 1.49)
<Missing>	30	15	8	11	15	10	12	1.22	(0.46, 3.24)
Use of mechanical ventilation at randomization									
No	234	118	86	9	116	89	10	1.01	(0.74, 1.38)
Yes	30	16	7	NA	14	5	NA	0.8	(0.25, 2.56)
Baseline CRP group by median									
High (≥ median)	118	65	41	14	53	38	12	1.16	(0.74, 1.83)
Low (< median)	124	57	43	7	67	49	11	0.87	(0.56, 1.33)
<Missing>	22	12	9	12.5	10	7	9	1.02	(0.37, 2.83)



B

Baseline risk factors	Total n	Placebo n	Placebo Events	Placebo Median (day)	Efmarodocokin alfa n	Efmarodocokin alfa Events	Efmarodocokin alfa Median (day)	Hazard Ratio	95% Wald CI
All	266	134	93	10	132	100	10	1.15	(0.86, 1.54)
Baseline ordinal score									
3	104	47	44	5	57	53	5	0.82	(0.53, 1.27)
4	134	71	45	14	63	44	13	1.15	(0.75, 1.76)
5−6	23	13	4	NA	10	3	NA	0.93	(0.21, 4.18)
<Missing>	5	3	0	NA	2	0	NA	NA	(NA, NA)
Baseline BMI									
<30	99	54	34	11.5	45	34	9	1.3	(0.79, 2.12)
≥30 to < 40	113	55	42	10	58	43	11	0.91	(0.58, 1.41)
≥40	21	10	9	12	11	10	7	1.34	(0.5, 3.54)
<Missing>	33	15	8	11	18	13	8.5	1.65	(0.66, 4.13)
Use of mechanical ventilation at randomization									
No	236	118	86	9	118	94	9	1.14	(0.84, 1.55)
Yes	30	16	7	NA	14	6	NA	1.02	(0.34, 3.06)
Baseline CRP group by median									
High (≥ median)	131	65	41	14	66	47	13.5	1.14	(0.74, 1.75)
Low (< median)	117	57	43	7	60	48	8	1.13	(0.73, 1.74)
<Missing>	18	12	9	12.5	6	5	8	1.67	(0.52, 5.35)

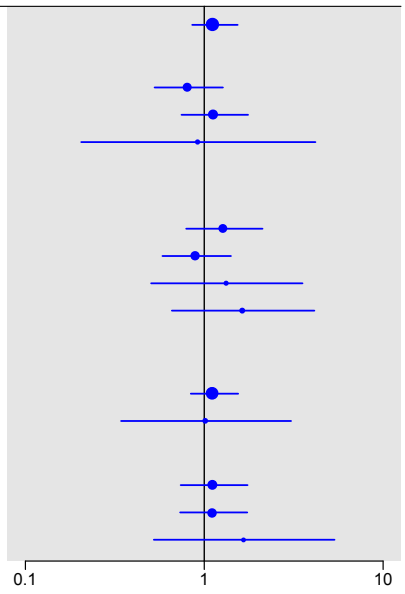


Figure S1. Time to recovery by baseline ordinal score (prespecified), baseline BMI, use of mechanical ventilation at randomization (prespecified), and baseline CRP subgroups for (**A**) astegolimab-treated and (**B**) efmarodocokin alfa-treated patients.

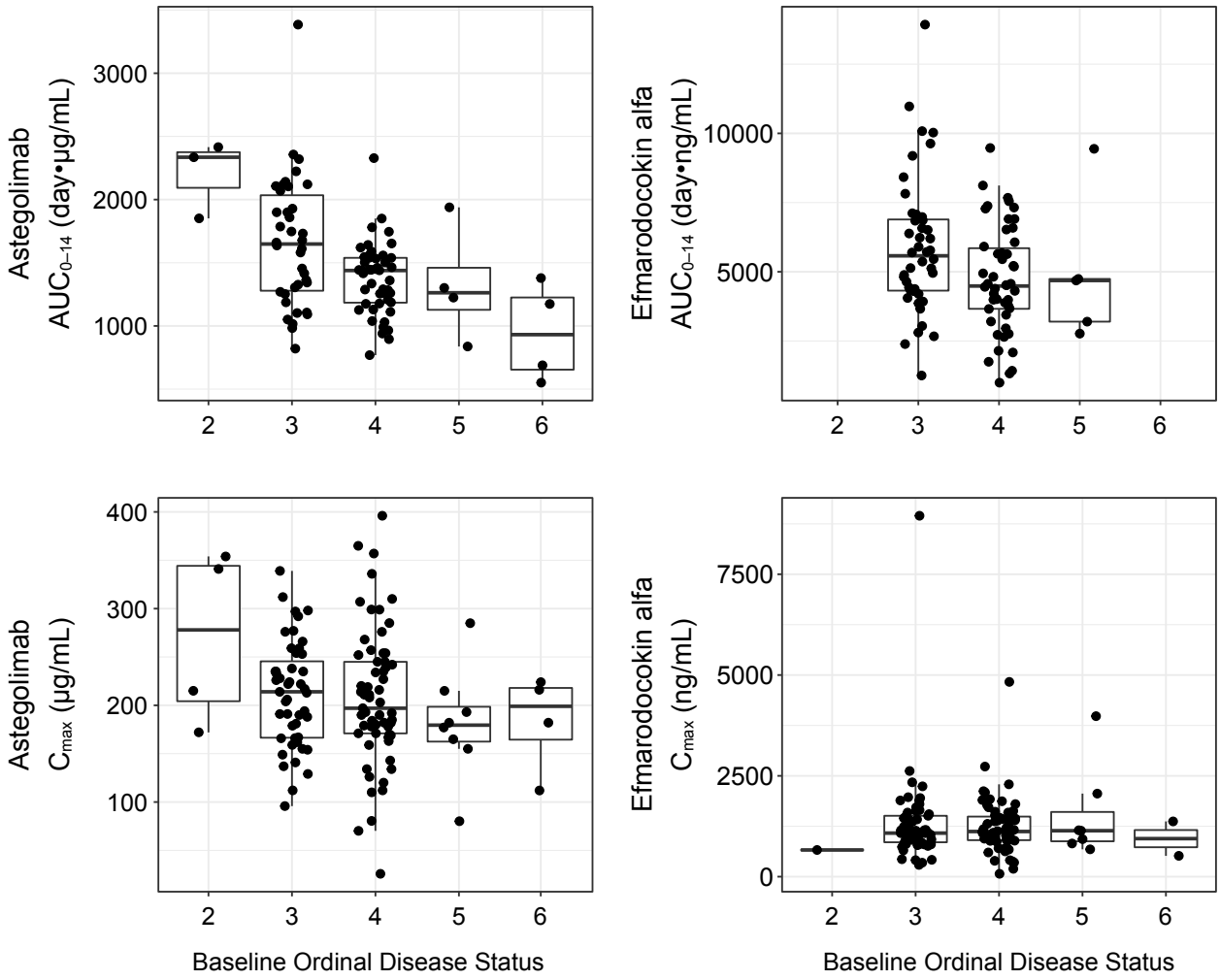


Figure S2. Effect of disease severity on astegolimab and efmarodocokin alfa pharmacokinetic parameters.
AUC_{0-14} = area under the concentration-time curve from day 0 to day 14.

Supplementary Tables

Table S1. Additional demographics

Characteristic	Placebo[a] (n=134)	Astegolimab (n=130)	Efmarodocokin alfa (n=132)	All patients (N=396)
Ethnicity, n (%)				
Hispanic or Latino	77 (57)	72 (55)	70 (53)	219 (55)
Not Hispanic or Latino	53 (40)	53 (41)	58 (44)	164 (41)
Not reported	4 (3)	1 (1)	1 (1)	6 (2)
Unknown	0	4 (3)	3 (2)	7 (2)
Race, n (%)				
American Indian or Alaska Native	2 (2)	4 (3)	0	6 (2)
Asian	6 (5)	4 (3)	5 (4)	15 (4)
Black or African American	10 (8)	7 (5)	10 (8)	27 (7)
Native Hawaiian or other Pacific Islander	0	4 (3)	1 (1)	5 (1)
White	92 (69)	87 (67)	89 (67)	268 (68)
Unknown	24 (18)	24 (19)	27 (21)	75 (19)
Country, n (%)				
Brazil	19 (14)	20 (15)	20 (15)	59 (15)
Mexico	14 (10)	23 (18)	17 (13)	54 (14)
Spain	16 (12)	13 (10)	15 (11)	44 (11)
United States	85 (63)	74 (57)	80 (61)	239 (60)

[a]Matching placebo groups for astegolimab and efmarodocokin alfa were pooled for all analyses.

Table S2. Additional secondary efficacy endpoints

Efficacy Endpoint	**Placebo[a] (n=134)**	**Astegolimab (n=130)**	**Efmarodocokin alfa (n=132)**
Time to improvement of at least 2 categories relative to baseline on a 7-category ordinal scale,[b] median days	10.0	11.0	10.0
HR (95% CI)		1.03 (0.77, 1.39)	1.15 (0.86, 1.55)
p value		0.84	0.34
Duration of supplemental oxygen, median days	18.00	17.00	13.50
Difference in medians		-1.00	-4.50
p value (Van Elteren test)		0.53	0.51
Clinical status assessed using 7-category ordinal scale at day 14,[b] median (95% CI)	1.0	1.0 (1.0, 1.0)	1.0 (1.0, 1.0)
Difference in medians		0	0
p value (Van Elteren test)		0.55	0.57
Clinical status assessed using 7-category ordinal scale at day 28,[b] median (95% CI)	1.0	1. 0 (1.0, 1.0)	1.0 (1.0, 1.0)
Difference in medians		0	0
p value (Van Elteren test)		0.34	0.47
Time to clinical failure,[c] median days		NE	NE
Patients with event, n (%)	37 (27.6)	40 (30.8)	33 (25.0)
HR (95% CI)		1.19 (0.76, 1.88)	0.92 (0.57, 1.48)
p value		0.45	0.72
Time to clinical improvement,[d] median days	5.5	6.0	6.0
HR (95% CI)		1.31 (0.71, 2.40)	1.18 (0.65, 2.15)
p value		0.38	0.59

CI = confidence interval, ECMO = extracorporeal membrane oxygenation, HR = hazard ratio, ICU = intensive care unit, NE = not evaluable, NEWS2 = National Early Warning Score 2.

[a]Matching placebo groups for astegolimab and efmarodocokin alfa were pooled for all analyses.

[b]Clinical status was defined by the 7-category ordinal scale:
1 - Discharged (or “ready for discharge” as evidenced by normal body temperature and respiratory rate, and stable oxygen saturation on ambient air or ≤2 L supplemental oxygen)
2 - Non-ICU (intensive care unit) hospital ward (or “ready for hospital ward”) not requiring supplemental oxygen
3 - Non-ICU hospital ward (or “ready for hospital ward”) requiring supplemental oxygen
4 - ICU or non-ICU hospital ward, requiring non-invasive ventilation or high-flow oxygen
5 - ICU, requiring intubation and mechanical ventilation
6 - ICU, requiring ECMO or mechanical ventilation and additional organ support (e.g., vasopressors, renal replacement therapy)
7 - Death

[c]Defined as the time to death, mechanical ventilation, ICU admission, or withdrawal of care. For patients entering the study already in ICU or on mechanical ventilation, clinical failure is defined as a one-category worsening on the ordinal scale, withdrawal, or death.

[d]Defined as a NEWS2 of ≤2 maintained for 24 hours

Supplementary Tables (cont.)

Table S3. Most common AEs (in ≥5% of patients) regardless of relatedness to study drug

	Placebo[a] (n=134)	**Astegolimab (n=130)**	**Efmarodocokin alfa (n=132)**	**All patients (N=396)**
No. of patients with ≥1 AE, n (%)	42 (31.3)	54 (41.5)	49 (37.1)	145 (36.6)
No. of AEs	75	95	92	262
MedDRA preferred term, n (%)				
Constipation	6 (4.5)	10 (7.7)	10 (7.6)	26 (6.6)
Hypokalemia	8 (6.0)	9 (6.9)	8 (6.1)	25 (6.3)
Anemia	7 (5.2)	9 (6.9)	7 (5.3)	23 (5.8)
Hypotension	7 (5.2)	9 (6.9)	7 (5.3)	23 (5.8)
COVID-19 pneumonia	7 (5.2)	8 (6.2)	5 (3.8)	20 (5.1)
Acute kidney injury	7 (5.2)	5 (3.8)	6 (4.5)	18 (4.5)
Dry skin	5 (3.7)	4 (3.1)	9 (6.8)	18 (4.5)
Atrial fibrillation	2 (1.5)	8 (6.2)	6 (4.5)	16 (4.0)
Headache	4 (3.0)	7 (5.4)	4 (3.0)	15 (3.8)
Hypertension	5 (3.7)	8 (6.2)	2 (1.5)	15 (3.8)
Anxiety	1 (0.7)	5 (3.8)	8 (6.1)	14 (3.5)
Nausea	2 (1.5)	3 (2.3)	7 (5.3)	12 (3.0)
Urinary tract infection	4 (3.0)	1 (0.8)	7 (5.3)	12 (3.0)
Pneumothorax	7 (5.2)	3 (2.3)	1 (0.8)	11 (2.8)

AE = adverse event. AEs were classified according to the Medical Dictionary for Regulatory Activities (MedDRA) v. 23.0.

[a]Matching placebo groups for astegolimab and efmarodocokin alfa were pooled for all analyses.

Supplementary Tables (cont.)

Table S4. Serious adverse events (SAEs)

	Placebo[a] (n=134)	Astegolimab (n=130)	Efmarodocokin alfa (n=132)	All patients (N=396)
Any event, n (%)				
Overall	38 (28.4)	38 (29.2)	34 (25.8)	110 (27.8)
Infections and infestations, n (%)				
Overall	19 (14.2)	18 (13.8)	15 (11.4)	52 (13.1)
COVID-19 pneumonia	5 (3.7)	7 (5.4)	5 (3.8)	17 (4.3)
Septic shock	3 (2.2)	3 (2.3)	4 (3)	10 (2.5)
COVID-19	2 (1.5)	3 (2.3)	1 (0.8)	6 (1.5)
Pneumonia	1 (0.7)	3 (2.3)	0	4 (1)
Urinary tract infection	0	1 (0.8)	2 (1.5)	3 (0.8)
Cellulitis	0	0	2 (1.5)	2 (0.5)
Pneumonia bacterial	1 (0.7)	1 (0.8)	0	2 (0.5)
Pulmonary sepsis	2 (1.5)	0	0	2 (0.5)
Sepsis	0	0	2 (1.5)	2 (0.5)
Respiratory, thoracic and mediastinal disorders, n (%)				
Overall	12 (9)	13 (10)	16 (12.1)	41 (10.4)
Respiratory failure	5 (3.7)	4 (3.1)	2 (1.5)	11 (2.8)
Pneumothorax	5 (3.7)	2 (1.5)	0	7 (1.8)
Pulmonary embolism	3 (2.2)	1 (0.8)	2 (1.5)	6 (1.5)
Acute respiratory failure	0	1 (0.8)	4 (3)	5 (1.3)
Hypoxia	0	2 (1.5)	3 (2.3)	5 (1.3)
Acute respiratory distress syndrome	1 (0.7)	0	2 (1.5)	3 (0.8)
Pneumonia aspiration	0	1 (0.8)	1 (0.8)	2 (0.5)
Respiratory distress	0	1 (0.8)	1 (0.8)	2 (0.5)
Cardiac disorders, n (%)				
Overall	9 (6.7)	5 (3.8)	3 (2.3)	17 (4.3)
Cardio-respiratory arrest	5 (3.7)	0	1 (0.8)	6 (1.5)
Atrial fibrillation	2 (1.5)	3 (2.3)	0	5 (1.3)
Cardiac arrest	1 (0.7)	1 (0.8)	2 (1.5)	4 (1)
Acute myocardial infarction	0	2 (1.5)	0	2 (0.5)
Cardiac failure	1 (0.7)	1 (0.8)	0	2 (0.5)
Renal and urinary disorders, n (%)				
Overall	6 (4.5)	4 (3.1)	6 (4.5)	16 (4)
Acute kidney injury	2 (1.5)	2 (1.5)	3 (2.3)	7 (1.8)
Renal failure	2 (1.5)	0	2 (1.5)	4 (1)
Renal impairment	2 (1.5)	1 (0.8)	1 (0.8)	4 (1)
Vascular disorders, n (%)				
Overall	2 (1.5)	3 (2.3)	5 (3.8)	10 (2.5)
Hypotension	2 (1.5)	2 (1.5)	2 (1.5)	6 (1.5)
Shock	0	1 (0.8)	1 (0.8)	2 (0.5)
Gastrointestinal disorders, n (%)				
Overall	2 (1.5)	2 (1.5)	2 (1.5)	6 (1.5)
Gastric ulcer hemorrhage	1 (0.7)	2 (1.5)	0	3 (0.8)
Gastrointestinal hemorrhage	1 (0.7)	0	2 (1.5)	3 (0.8)
General disorders and administration site conditions, n (%)				
Overall	1 (0.7)	2 (1.5)	2 (1.5)	5 (1.3)
Multiple organ dysfunction syndrome	1 (0.7)	2 (1.5)	1 (0.8)	4 (1)
Psychiatric disorders, n (%)				
Overall	0	1 (0.8)	1 (0.8)	2 (0.5)
Confusional state	0	1 (0.8)	1 (0.8)	2 (0.5)

Table S4. Serious adverse events (SAEs)

[a]Matching placebo groups for astegolimab and efmarodocokin alfa were pooled for all analyses.
The following SAEs occurred in only one patient each:
Placebo: bacillus bacteremia, bacteremia, Candida sepsis, orchitis, pneumonia klebsiella, pneumonia pseudomonal, pneumonia staphylococcal, superinfection bacterial, supraventricular tachycardia, hypertension, hepatic enzyme increased, liver function test increased, hyperkalemia, cerebrovascular accident, anemia, back pain
Astegolimab: urosepsis, pleural effusion, pneumomediastinum, respiratory arrest, left ventricular failure, right ventricular dysfunction, hematuria, shock hemorrhagic, aspartate aminotransferase increased, oxygen saturation decreased, radius fracture, hypernatremia, toxic encephalopathy, liver injury, uterine leiomyoma
Efmarodocokin alfa: device related sepsis, dyspnea, urinary incontinence, distributive shock, peripheral ischemia, anal incontinence, ill-defined disorder, fall

Supplementary Tables (cont.)

Table S5. Summary of serum pharmacokinetic parameters by treatment

	Statistics	**C_{max_first} (µg/mL)**	**AUC_{0-14} (day•µg/mL)**	**$C_{trough\_day\ 14}$ (µg/mL)**
Astegolimab 700 mg IV	n	119	94	30
	Mean ± SD	210 ± 65.0	1494 ± 446	33.5 ± 16.6
	Statistics	**C_{max_first} (ng/mL)**	**AUC_{0-14} (day•ng/mL)**	**$C_{trough\_day\ 14}$ (ng/mL)**
Efmarodocokin alfa 90 µg/kg IV	n	130	99	28
	Mean ± SD	1286 ± 933	5238 ± 2274	81.8 ± 41.9

AUC_{0-14} = area under the concentration-time curve from day 0 to day 14, C_{max_first} = maximum concentration after the first dose, $C_{trough\_day\ 14}$ = trough concentration after the first dose on day 14 before the second dose, IV = intravenous.

Table S6. Baseline levels of sST2 and REG3A

	Placebo[a] (n=129)	**Astegolimab (n=123)**	**Efmarodocokin alfa (n=130)**	**Overall (N=382)**
sST2 (ng/mL)				
n	125	123	129	377
Mean ± SD	116 ± 101	103 ± 69.1	129 ± 168	116 ± 121
REG3A (ng/mL)				
n	113	116	119	348
Mean ± SD	14.1 ± 13.3	15.4 ± 16.2	15.8 ± 22.2	15.1 ± 17.7

REG3A = regenerating islet-derived protein 3A, SD = standard deviation, sST2 = soluble ST2.

[a]Matching placebo groups for astegolimab and efmarodocokin alfa were pooled for all analyses.

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